

## Possible physiological and pathophysiological consequences of the nonuniform distribution of the formed elements of blood. Part two: expanded discussion.

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**Abstract:** Both in-vitro and in-vivo observations and experiments show that the radial distribution of formed elements in blood flowing in arteries is, under certain circumstances, not uniform. The non-uniform distribution of the vast majority component in blood cells, erythrocytes, is related with a spatial variation in blood viscosity and modifications in blood shear rates. The variations both in shear rates and in blood cell concentrations near the endothelium, modifies fluid-to-wall mass transport processes in arteries.

The purpose of this article is:

(a) Discuss conditions for in vivo appearance of the axial accumulation of red cells, considered as one of the self-fluidization mechanisms of moving blood in the arterial conduits. Discuss the non-uniform distribution of the other formed elements (platelets and leukocytes).

(b) Analyze possible consequences and physiological and pathological interrelationships of these phenomena. Some biomechanical aspects of growth, remodeling, and damage in arterial walls during the life cycle are considered.

The discussion is framed in the relation between hemodynamics, an optimum principle (Bejan's constructal law) and the biomechanics of the arterial wall (considered as a local mechanical unit). Both short and long terms modifications in the geometric and mechanical properties of the arterial wall and the mechanisms of vascular control and the geometry of the arterial wall are considered.

The self-fluidification of blood at high shear rates and the self-impeding of flow at low shear rates are considered as non-equilibrium phase transition.

The association between changes in blood rheology and cardiovascular risk factors, including psychological stress and psychiatric illness are related in the framework of psycho-immuno-neuroendocrinology.

Then the subject is considered from the point of view of evolutionary biology.

Aggregation as a mechanism that intensifies the axial accumulation of erythrocytes and reinforces the self-fluidization properties of blood is observed in athletic species but not in sedentary species.

In athletic species, such as homo sapiens, the increase in oxygen demand may require a significant increase in the flow that supplies certain tissues.

This allows us to give an evolutionary interpretation to the increased velocity profile that produces the disaggregation of erythrocytes and reduces the viscosity of the blood in arteries and in veins.

**Keywords:** Optimum principles. Biological evolution. Non-equilibrium phase transitions. Cardiovascular physiology and pathophysiology. Blood rheology. Non uniform radial distribution of blood formed elements. Mass transport processes. Arteriosclerosis. Atherosclerosis. Athletic species. Psycho-immuno-neuroendocrinology. Psychological and psychiatric cardiovascular risk factors.

## (1) Introduction

Let us begin with a brief review of blood rheology and related topics.

Blood is a suspension of cells, called formed elements (erythrocytes, the majority, leukocytes, and platelets) in plasma, an aqueous solution of electrolytes and nonelectrolytes (inorganic and organic ions, neutral organic molecules, and macromolecules).

From the rheological point of view, plasma can be considered as a Newtonian fluid (whose viscosity  $\eta$  is independent of the shear rate  $\dot{\gamma}$  but depends on the concentrations of dissolved substances), while blood behaves in general as a non-Newtonian fluid, whose viscosity depends on both shear rate and hematocrit  $\phi$  (the concentration of formed elements, determined by erythrocytes) (Cokelet and Meiselman, 2007; Cowan et al, 2012; Schmid-Schönbein, 1996).

Figure 1 shows the relation between shear stress  $\tau$  and shear rate  $\dot{\gamma}$  for whole blood, and how the viscosity of blood measured in viscometers decreases as the shear rate increases (shear thinning).

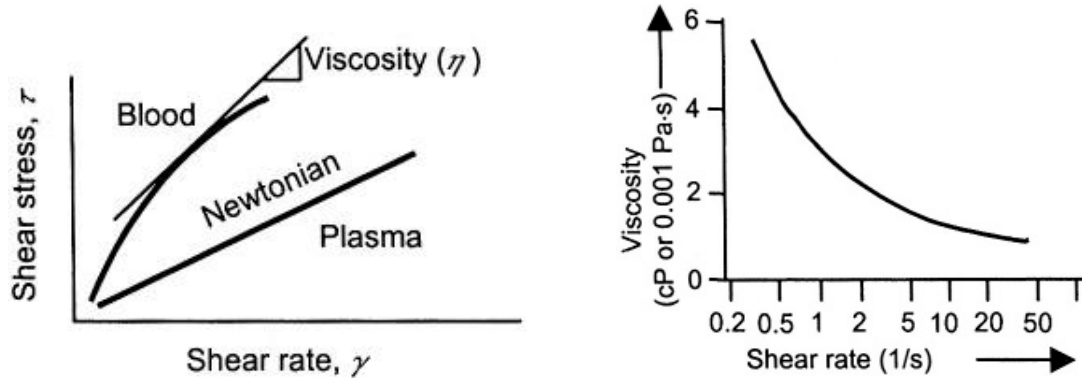


**Figure 1. Left: a comparison between the behavior of the constitutive relations (stress versus strain rate) of whole blood and of plasma. In case of blood the relation between shear stress and shear strain rate is nonlinear. So, a variable viscosity is defined as  $\eta = \frac{\Delta\tau}{\Delta\dot{\gamma}}$ . This is suggested by the small triangle that appears in the figure and measures the slope of the tangent to the curve  $\tau$  versus  $\dot{\gamma}$  at a certain value of the strain rate. Right: the relation between apparent blood viscosity and shear rate for a hematocrit of  $\phi = 0.48\%$  (Modified from Westerhof, Stergiopulos and Noble, 2005).**

At low enough shear rates, erythrocytes under normal conditions tend to pile up in aggregates (rouleaux).

At rest, the rouleaux combine into a three-dimensional network, the rupture of which generally appears to require overcoming a threshold shear stress (yield stress) dependent on the protein content (especially fibrinogen concentration) of the plasma.

Figure 2 (left) shows a structure formed by aggregates of erythrocytes. Figure 2 (right) suggests how erythrocytes behave as the shear rate increases.

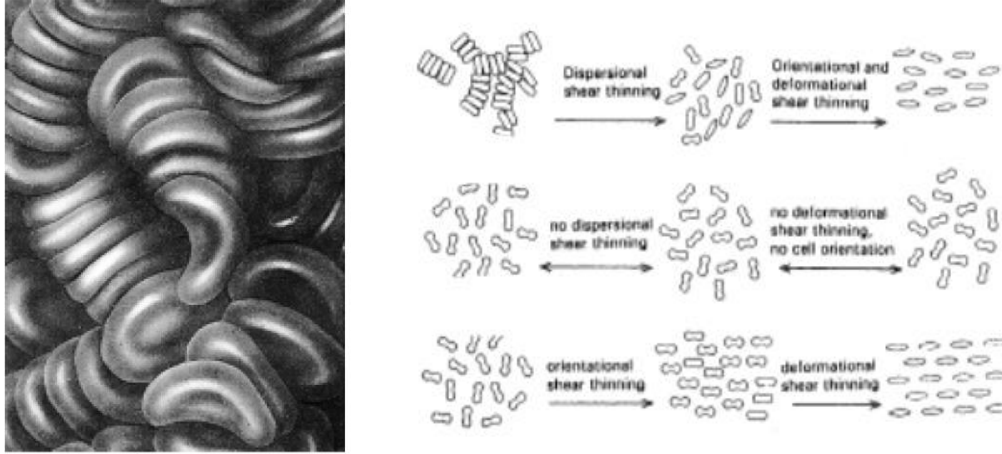


**Figure 2. Left: Aggregate of erythrocytes (taken from Exempla Hämorheologica, Albert Roussel Pharma GmbH, Wiesbaden, Germany, 1980). Right (modified from Schmid-Schönbein, 1996): diagram of the processes of disaggregation of rouleaux, orientation and deformation of erythrocytes during blood flow in vessels. The upper part of the diagram shows the behavior of normal erythrocytes in plasma. The middle part shows hardened erythrocytes in a watery solution with 11 % of albumin. The lower part shows the behavior of normal erythrocytes also in a watery solution with 11 % of albumin.**

On the other hand, viscosity measurements show that it increases when the concentration of formed elements (the hematocrit) increases (Figure 3).

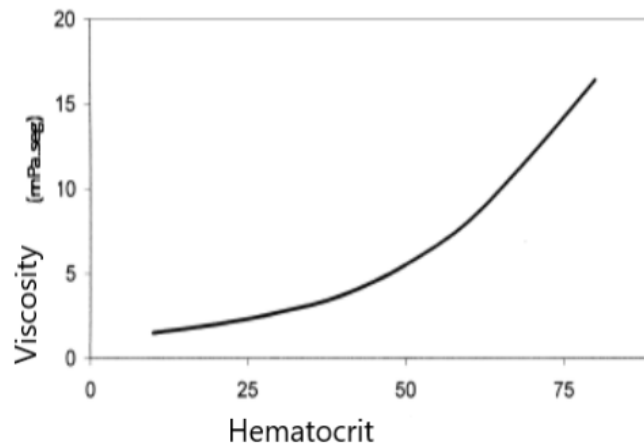


**Figure 3. Increase in blood viscosity (in mPa×s) with increasing hematocrit (in %), for a constant shear rate.**

Both effects combine to, given a plasma viscosity, determine the viscosity of the blood flowing in the arteries. What was said about the constitutive relation between shear stress and shear strain rate for blood can be summarized by the formula:

$$\tau(\phi, \dot{\gamma}) = \eta_{app}(\phi, \dot{\gamma}) \dot{\gamma}$$

An apparent viscosity  $\eta_{app}(\phi, \dot{\gamma}) = \frac{\tau}{\dot{\gamma}}$  was introduced to relate stress with rate of strain.

This is a function  $\eta_{app}$  that increases with the hematocrit and decreases with shear strain

rate, as explained above. For plasma, the apparent viscosity is the true viscosity of the fluid and is independent of the shear strain rate.

Figure 4 shows a velocity profile in the vicinity of an arterial wall, with axial  $v_{axial}$  and  $v_{circ}$  circumferential components of the blood velocity vector  $\vec{v}$  at different vertical distances from the inner surface of the vessel wall (the radial component of velocity is assumed to be zero). The distances are taken on a half straight line through the normal unit vector  $\vec{n}$ .

The axial  $\tau_{axial}$  and circumferential  $\tau_{circ}$  components of the shear stress vector  $\vec{\tau}$  that the fluid exerts on the wall were drawn on the inner surface of the vessel wall.

Furthermore (although it does not appear in Figure 4), a fluid pressure acts on the wall at each point, parallel to the corresponding normal unit vector  $\vec{n}$  (the latter does appear in Figure 4 together with the axial  $\hat{e}_{axial}$  and circumferential  $\hat{e}_{circ}$  unit vectors).

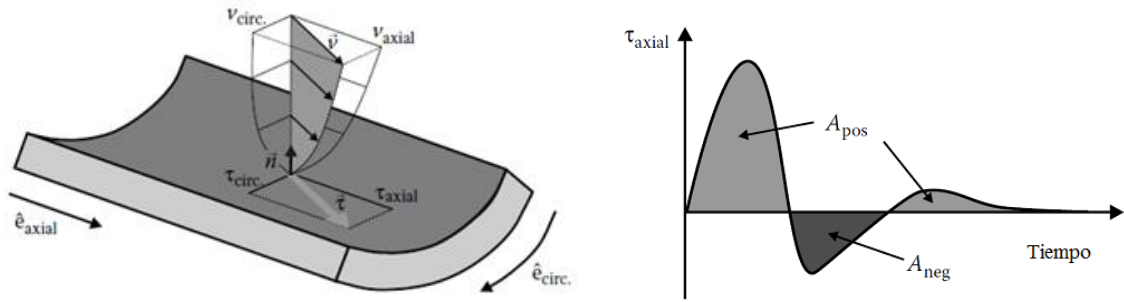


**Figure 4 (Modified from Suárez-Antola and Suárez-Bagnasco, 2015)** Left: a diagram of the velocity profile near the vessel wall and the shear stress vector on the inner surface of the vessel wall, with its two components, axial and circumferential. Right: a sketch of a possible time variation in the axial component of the shear stress vector at the same point of the inner surface of the wall, during a cardiac cycle.

As blood wets the walls of the arteries, the tangential component of velocity over the wall is canceled. The magnitude of blood velocity increases in the radial direction when the considered point moves away from the wall, as shown in Figure 4 (Left), and a radial gradient of velocity results.

The tangential stress component on the wall is in general different from zero, and in certain locations can oscillate as shown in Figure 4 (Right) depending on the behavior of the radial gradient of blood velocity near the wall.

When the output increases during systole, the velocity must increase in the central zone of the flow. Then the radial velocity gradient (and hence the shear velocity) increases in turn, especially in the vicinity of the wall.

In contrast, when output decreases during diastole, shear rates decrease.

The increase in the field of shear rates increases the degree of dissociation of the erythrocyte aggregates, orients them in the flow and increases the deformation of these blood cells, with which the viscosity of the blood decreases.

Decreasing flow has the opposite effect, which is why it is associated with an increase in viscosity.

Therefore, due to the fluidifying effect of the increase in shear stress, for a constant and spatially uniform hematocrit, it is expected that a field of local viscosities will be installed that takes lower values near the arterial wall and higher values near the axis of the flow.

The hematocrit can vary, in the same instant, from one point to another of the same cross section to the flow.

In-vitro and in-vivo observations (from the 18th century and during the 19th century), as well as various in-vitro and in-vivo experimental investigations carried out in the 20th century <sup>1</sup> and so far in the 21<sup>st</sup> by powerful imaging methods (Labrosse and Kadem, 2019), have provided evidence about that the spatial distribution of erythrocytes, leukocytes and platelets present in the blood flowing within the arteries may not be uniform (Baskurt and Meiselman, 2007; Baskurt and Meiselman, 2013; Schmid-Schönbein, 1996; Suárez-Antola, 1980).

The digital simulations of the flows in realistic geometries are possible since the end of the last century, due both to the appearance of computers with the adequate calculation capacity and to the availability of calculation codes.

These codes are suitable to simulate in silico and with some fidelity, the behavior of complex biomechanical dynamic systems with distributed parameters (Auricchio et al, 2019; Rodney and Doyle, 2017) including an increasing capability for patient specific modelling (Hoskins et al, 2017).

The application of these computational tools confirms the afore mentioned experimental results on the migration of blood cells induced by shear deformations and related mechanisms (Biasetti J et al, 2014).

Thus, there is both experimental and computational evidence that, in addition to the thin layer of blood cell-free plasma that is always adjacent to the endothelium, there is usually a spatial variation in the distribution of blood cells within the vessel lumen in the same cross-section and in the same instant, the hematocrit being higher near the axis and lower near the wall.

A hematocrit that decreases towards the wall is associated with a viscosity that also decreases as we approach the endothelium.

An increase in shear rate together with a decrease in hematocrit as we approach the wall, act synergistically to decrease the local viscosity of blood, and generate a field of varying viscosities.

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<sup>1</sup> Haller and Spallanzani found, as early as the 18th century, during in-vivo observations in animal mesenteric arteries, that blood cells tend to accumulate around the axis of the vessels. In 1941, Müller observed the same behavior in-vitro, in a straight capillary tube through which he had established a steady laminar flow of a glycerol solution with a suspension of rubber micro-discs (of the same density as the fluid to eliminate the gravitational field effects) (Taylor, 1955; Bayliss, 1959).

Next to the arterial wall the field of shear velocities influences the mass transport between the fluid and the endothelium through the convection-diffusion boundary layer adjacent to the endothelium (Coppola and Caro, 2009).

This influence must be considered when the limiting mass transport step is in this boundary layer, as appears to occur with the transport of oxygen, ATP, bradykinin, angiotensin, and other effectors (which are degraded or chemically modified on the surface of the endothelium) (Tarbell and Qiu, 2006).

If the rate-limiting step for transport is in the endothelium, as occurs with cholesterol, the response of its cells to the mechanical stresses produced because of the fluid-structure interaction acquires relevance. These stresses are composed of the pulsatile or oscillating shear stresses produced by blood flow over the wall, and the pulsatile stresses within the arterial wall.

This response is accompanied by a modification in the permeability of the endothelium and influences the changes that occur in the structure of the arterial wall.

In sum, spatial variations in blood viscosity directly affect hemodynamics, and indirectly the transport processes between the blood and the wall.

In the first part of the present investigation and in a previous conference paper, both of a physical-mathematical nature, a simple mathematical model was built and analyzed, which considers the spatial variations of the viscosity transverse to the flow axis (Suárez Ántola and Suárez-Bagnasco, 2015).

The artery segment was represented by a cylinder with a circular cross-section, with a rigid wall, in the absence of a gravitational field, with axisymmetric flow, to simplify the analysis.

The effects of different rheological models with position-dependent hematocrit, with shear thinning (Quemada model) and without shear thinning (generalized Newtonian model) were investigated.

Quasi-stationary conditions were considered for the application of analytical methods. When the latter are not met, it is necessary to resort to digital simulation methods.

To verify the limits of validity of the quasi-stationary approximation and to investigate what happens when this condition is not applicable, some results obtained by numerical calculation using the finite element method to calculate the velocity profiles and shear stresses were summarized (Suárez-Bagnasco and Suárez Ántola, 2014; Suárez Ántola and Suárez-Bagnasco, 2015).

The results obtained in the first part (Suárez-Bagnasco and Suárez Ántola, 2014; Suárez Ántola and Suárez-Bagnasco, 2015), in agreement with the evidence provided in other recent works (Apostolidis and Beris, 2015; Moreno et al, 2015; Apostolidis, Armstrong and Beris, 2015; Biasetti et al, 2014) suggest that taking into account the non-Newtonian rheological properties of blood (and in particular, the spatial variations of the viscosity associated with the axial accumulation of the formed elements) in the mathematical models, both analytical and numerical, can significantly modify the de-

scription of the local hemodynamics obtained, the results of the quantification of the processes of mass transport between the fluid and the arterial wall, and the estimation of the power required to maintain a pulsatile flow in an artery, compared to what is obtained, for the same flow, when working with a Newtonian fluid whose viscosity remains constant.

Now it is necessary to discuss to what extent the deterministic correlations, both analytical and numerical, presented in the previous work, correspond to what can happen in the systemic circulation.

In any case, the afore mentioned mathematical model could be considered as a highly idealized representation of the axial accumulation produced in a flow of blood in vertical glass tubes. (Most of the laboratory research on the rheological properties of blood during the 20th century was carried out on these tubes (Rampling, 2007).

In horizontal tubes, the difference in density between erythrocytes and plasma (less dense than erythrocytes) can produce a significant degree of sedimentation of erythrocyte aggregates towards the bottom of the tube, with the consequent destruction of the symmetry assumed in the model.

Tubes of sufficiently long lengths are required for axial accumulation to manifest when the red cells in the incoming blood are evenly distributed.

The arteries of the circulatory system curve, divide, subdivide, and converge in all directions. It is to be expected that their lengths are not always sufficient for an axial accumulation of red cells to develop fully.

To this must be added the inertial effects on the flows, caused by body movements (Noordergraaf, 2011), and the changes in the geometry of the arteries due to changes in position sustained over time, such as those that can occur during sleep.

In vivo blood flow interacts with the compliant and remodeling wall of the arteries.

This wall has a complex structure of three tunics (intima, media, and adventitia) to which it has recently been proposed to add a fourth (adipose) (Suárez-Bagnasco, 2014).

The cellular components of these tunics (endothelial cells, muscle cells, fibroblasts, adipocytes, immune cells, and nerve endings) interact with each other and with the extracellular matrices, in a continuous exchange of molecular signals.

The smooth musculature of the wall is finely innervated.

The tunica adipose, the adventitia, and the external part of the tunica media are supplied by the vasa vasorum (Gössl et al, 2003).

Through the lumen (which interacts with the vascular endothelium and through the endothelium with the rest of the intima and the region proximal to the lumen of the tunica media) and the vasa vasorum, the wall exchanges endocrine and immune signals with the rest of the body and responds to the modifications that its micro-environment undergoes.

For the same volumetric flow rate, the distribution of blood velocities in the arterial lumen and the associated shear velocity field (field that induces the migration of the

formed elements), will vary with changes in the geometry of the channel, anatomical or functional (vasoconstriction or vasodilation).

Thus, it is not surprising that the conditions for axial accumulation of erythrocytes in the arteries of an organism may differ significantly from the conditions for such accumulation studied in tubes.

This second part of a biomedical nature is intended to put in a broader perspective and discuss the results of the first part and of other investigations on the relationships between hemorheology and hemodynamics, in a biophysical, physiological, and pathophysiological framework.

-In section 2 we briefly consider a general thermodynamic principle of organization of flows, applicable in arterial hemodynamics, known as Bejan's constructal law. Being an optimum principle, the details of the physical mechanisms that allow optimizing the flows by system remodeling are outside the scope of this approach.

-In section 3 we review the properties of arterial wall biomechanics and its relations with blood flow control, keeping in mind what is necessary for the investigation of the non-uniform distribution of the formed elements of the blood. Now the accent is on the mechanisms that make possible modifications in the behavior of the vascular system under varying circumstances. The arterial wall is considered first as a local mechanical unit. After that, we consider short and long-term modifications in the geometric and mechanical properties of the arterial wall. The section ends with an appraisal of vascular control mechanisms and their relationship with the modifications in artery wall geometry.

-In section 4 the axial accumulation of erythrocytes and the self-fluidization of blood is considered. Besides the origins of the non-uniform distribution of the other formed elements are discussed.

-In section 5 the characterization of some rheological phenomena in the framework of non-equilibrium phase transitions is briefly discussed first.

Then the association between changes in blood rheology and cardiovascular risk factors, including psychological stress and psychiatric illness are discussed in a framework afforded by psycho-immuno-neuroendocrinology.

-In section 6 the subject is considered from the point of view of evolutionary biology, introducing a distinction between athletic biological species and sedentary biological species.

This distinction allows us to give an evolutionary interpretation to the increased velocity profile that produces the disaggregation of erythrocytes and reduces the viscosity of the blood in the in cardiovascular conduits.

-In section 7 some conclusions are highlighted.

## **(2) Hemodynamics and Optimum Principles in Physiology**

The flow of blood through the ducts of the arterial tree constitutes a system of flows with configurations (geometries) endowed with a certain degree of flexibility but complying with certain restrictions.

The generation of the flow configuration in a natural system, such as the circulatory system, as time passes, is a phenomenon that complies with a law formulated by Adrian Bejan in 1996: so that a finite-dimensional system can persist over time must evolve in such a way that the system provides easier access to the imposed global currents that flow through that system (Bejan, 2007).

When the global current is fixed, the constructive objective that emerges from the law of evolution of flow configurations is a flow architecture that allows this global current with a minimum global driving pressure difference, or equivalently, with minimal overall resistance, or with minimal frictional entropy generation.

However, once all the internal constraints to an isolated material system have been removed, the second law of thermodynamics states that it will evolve towards a state of equilibrium.

Because of this, constraints such as a fixed global flow are necessary to move the system away from thermodynamic equilibrium, and to be able to keep it away from equilibrium.

Bejan's law states that in an open material system, with imposed global currents, there is a stationary flow architecture, defined as the configuration for which all the possibilities of increasing the access of flows and the freedom to reconfigure themselves has exhausted.

It is a law of non-equilibrium thermodynamics.

As it is a thermodynamic law, it does not provide information on the mechanisms that are put into play in each case to make the evolution of architecture possible, in the sense established by law.

A consequence of Bejan's law is that the way to connect a point (source or sink of a flow) with an infinite number of points (sinks or flow sources respectively) with minimal power dissipation is by means of a pipe tree (Bejan, 2007).

In the case of the circulatory tree, the minimum building block size is given by the Krogh functional unit (Krogh's pericapillary cylinder) (Barrett et al, 2019).

In the pericapillary region is located the slowest mode of transport: transport through the extracellular matrix and tissue cells, passive and active.

These minimal blocks cover the entire system (all the irrigated tissues of the body) including the arterial walls but excluding the lumen of the tree ducts.

The modes of transport with decreasing resistance appear in successive blocks of greater size (capillaries, arterioles, small arteries, and large arteries until reaching the aorta).

If the geometry of each building block is optimized to minimize the access resistance from a point to a region, a tree of ducts, the angle between the branches, and the dimensions and shapes of the cross-sections of each duct can be deduced.

For the angle between branches and for the relationship between the diameter of the trunk of a branching intermediate artery and the diameters of its branches, the results known as Murray's laws are obtained.<sup>2</sup>

According to Bejan's law, if a conduit can modify the geometric shape and dimensions of its cross sections, then as time passes those shapes will evolve so that the currents that flow through those conduits flow with less resistance.

This evolution is observed in the case of blood flow in the arteries, during the entire life cycle, from the embryonic stage to the adult stage and old age.

It occurs through mechanisms of growth and remodeling of the arterial wall that are briefly described below.

### **(3) A review of arterial wall biomechanics and its relations with blood flow control.**

#### **(3.1) The arterial wall considered as a local mechanical unit**

Non-uniform growth of the arterial wall leads to the appearance of residual mechanical stresses. These stresses do not disappear when the pressure difference across the wall due to pressurization in the lumen and the traction force due to the tissues adjacent to the tunica adventitia, to which the latter is anchored, are eliminated.

In an arterial wall of an artery separated from the tissues that surround it in the body and discharged, the residual circumferential stresses are evidenced by separating a ring from the discharged wall and making a radial cut: it generally opens spontaneously or coils a little about himself (Thubrikar, 2007).

Figure 5 shows a case of opening a wall ring, which releases residual stresses.

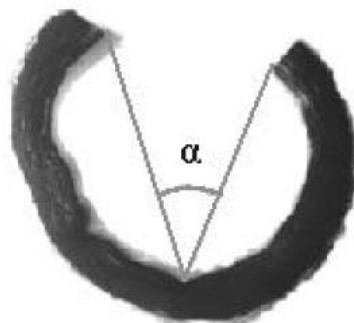


**Figure 5. Opening of a common carotid artery ring after making a radial cut. One of the ways to define an opening angle  $\alpha$  (van Leeuwen, 2003) is represented.**

<sup>2</sup> On Murray's laws and some of his later generalizations see Lubashevsky and Gafiychuk, 1999; Painter et al, 2006; Wagenseil and Mecham, 2009.

The residual stress system is not only modified during the remodeling of an artery in an adult organism, but it already arises inside the wall of the vessels during the development of the organism, accompanying the appearance in the embryo, of a circulation in oscillatory regime in a pressurized system. When combined with the circumferential stresses produced by the pressurization of the vessel, they result in a approximately uniform distribution of these stresses, advancing radially from the lumen towards the adventitia (Gleason et al, 2004).

A decrease in flow to sufficiently small values has been observed in the embryo, leading to a shrinkage and subsequent regression of the vessels (Hahn and Schwartz, 2009). This effect seems to be associated with low shear stresses produced by the flow of embryonic blood on the endothelium of the vascular wall.

In the developed organism, vascular remodeling phenomena (variations in the diameter of the vessel, the thickness, and the structure of the vascular wall) are also associated with the afore mentioned shear stresses. Likewise, there is evidence that these remodeling phenomena are influenced by changes in stresses inside the vascular walls (Nadasy, 2012; Thubrikar, 2007).

After the heart begins to beat and the blood cells enter the circulation, the primitive proto-vascular network is reorganized into a typical vascular tree in which the great arteries branch into smaller arteries and these into capillaries that meet to form veins. In this embryonic development, the effects of the pressure of the fluid contained in the vessels and the shear stresses at the interface between the fluid and the structure seem to have a determining role, through the mechano-transduction effects that occur in the vascular wall. Using genetic, surgical, and biomechanical manipulations in an animal model, evidence has been found about the importance of shear stress for this reorganization of the primitive vascular plexus into a true hierarchical vascular system (Lucitti et al, 2007; Barresi and Gilbert, 2016).

The fact that all the cells of the arterial wall are linked to the extracellular matrix by their own internal fibrillar structure, makes the wall behave as a unit from the local mechanical point of view.

The mechanical stresses inside the wall bring about deformations that act as mechanical signals on the smooth muscle cells. In particular, the shear stresses that blood flow exerts on the endothelium produce deformations that extend into the wall and act as mechanical signals for endothelial cells (Hahn and Schwartz, 2009; Hsiai et al, 2010).

There is evidence that all these mechanical signals trigger metabolic changes in the endothelium and smooth muscle cells and influence the construction and adjustment (remodeling) of the arterial wall structure (Nadasy, 2012; Wagenseil and Mecham, 2009).

The mechanical stresses inside the wall are associated with corresponding deformations. Circumferential or tangential tensile stress is associated with an increase in the internal radius of the artery due to stretching in the circumferential direction.

Longitudinal traction stress is associated with a stretching of the arterial wall parallel to the axis of the artery.

Tangential and longitudinal deformations are accompanied by a variation in the wall thickness through radial deformation, which combines with tangential and longitudinal deformations and keeps the volume occupied by the wall material approximately constant. (Gleason et al, 2004; Nadasy, 2012; Wagenseil and Mecham, 2009).

### **(3.2) Short and long-term modifications in the geometric and mechanical properties of the arterial wall**

The mechanical behavior of the arterial wall can be considered on two-time scales of different orders of magnitude. A short-term scale associated with the cardiac cycle, and a long-term scale, associated with the growth and remodeling of tissues.

On the time scale associated with the cardiac cycle, the wall does not grow or remodel, but responds to pressure and flow variations in the lumen, deforming as previously described.

On a timescale of the order of minutes, responses to humoral and nervous signals are produced that modify cellular metabolism and alter the tone of the muscle tissue of the wall, but do not produce any detectable changes at the histological level.

On a long-term scale, all the mechanical parameters mentioned act as stimuli for the growth and remodeling of the arteries. Since all these parameters act interrelated, it is difficult to discriminate which parameters induce which response at the cellular level. But in general lines it seems that the geometric and mechanical properties of the vessels are regulated to keep the stresses and deformations within the physiological values and to minimize the energy dissipation associated with a level of flow required by the tissue metabolism.

Thoma summarized this regulation in three laws formulated from the anatomical study of vessels in cadavers (Wagenseil and Mecham, 2009):

- 1) The size of the lumen (the radius of the discharged artery) depends on the flow of blood carried.
- 2) The length of the vessel depends on the longitudinal force exerted by the surrounding connective tissues.
- 3) The thickness of the vessel wall depends on the pressure of the blood.

We describe these three dependency relationships below.

For a given flow and a given vessel radius, the shear stress acting on the wall increases as the viscosity of the blood increases. Then, all other conditions being equal, if the viscosity increases (decreases) the shear stress increases (decreases) and the energy dissipation increases (decreases). If the flow is maintained and the initially increased viscosity does not decrease on the time scale associated with growth and remodeling, the radius (of the discharged artery) increases due to remodeling of the wall, counteracting the effect of increased viscosity. On the other hand, if the flow through a vessel undergoes a considerable and sustained increase over time, its radius will increase so that the shear stress on the endothelium remains relatively constant (Wagenseil and Mecham, 2009), and the power dissipation does not increase.

The length of a vessel will depend on the longitudinal force exerted by the adjacent connective tissue. This length will vary, to keep the longitudinal stress within physiological limits.

Lastly, a vessel that operates at higher pressures, other conditions being equal, will have a thicker wall to keep the average circumferential stress within physiological values.

In sum, the complexities of the geometry of the arterial tree and the modifications in the pulsatile flow of blood, together with the modifications in the arterial walls<sup>3</sup>, lead to the fact that both the characteristics of the flow and the distribution and temporal course of the efforts of shear on the walls and the mechanical stresses internal to the arterial walls, vary from one region to another at the same moment, and during the aging process of the organism in the same vascular region.

### **(3.3) Vascular control mechanisms and artery wall geometry**

The control of blood flow that irrigates the tissues is conditioned by an order of priorities established at the level of the central nervous system, but normally operates tending to balance the supply and removal of metabolites with the tissue demand.

It manifests itself in a fine regulation of the state of contraction (tone) of the smooth muscle of the arterial wall, through two main mechanisms: the effect of the nerve endings that innervate the parietal muscle cells on the one hand, and through mediators such as nitric oxide, which dilate or contract the vessel, on the other.

Nitric oxide, a powerful vasodilator, is synthesized locally by endothelial cells. Its production increases when the shear stress that the blood flow exerts on the endothelium increases.

For a given pressure in the lumen and elastic characteristics of the wall, the tone of the parietal smooth muscle determines the increase or decrease of the radius of the vessel, with a corresponding increase or decrease in the flow supplied by the artery.

A modification in the rheological properties of the blood, such as a redistribution of the local hematocrit field (associated with axial accumulation of erythrocytes) or a modification in the viscosity of the plasma, generally modifies the shear stress on the endothelium. The radius of the artery will then be modified by variation in local nitric acid production unless local nervous regulation or other mediators counteract this effect.

In sum, in vivo, the control of the muscular tone of the wall, and therefore the control of the arterial diameter, is inextricably interrelated with hemodynamics and hemorheology.

### **(4) Axial accumulation of erythrocytes and self-fluidization of blood. Consequences of the non-uniform distribution of the other formed elements.**

The axial accumulation of erythrocytes is a manifestation of the tendency to self-lubricate exhibited by normal blood flowing through the arteries (Schmid-Schönbein et al, 1996).

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<sup>3</sup> Including the progressive increase in the stiffness of the walls, beginning in the aorta and continuing in the other great arteries, characteristic of the arterial aging process.

The migration mechanisms that move the deformable erythrocytes away from the vessel wall allow the plasma, the less viscous liquid, to be arranged adjacent to the arterial walls where the shear rate is higher, while a more viscous liquid suspension is configured towards the center of the conduit, where the shear rate is lower.

With this non-uniform distribution of the formed elements of the blood, the energy dissipation in an artery segment decrease compared to what it would have if they were uniformly distributed: the same flow can be maintained with a smaller pressure difference. In the adjacencies of the flow axis, or more generally in regions where shear rates are very small or null, erythrocytes can travel in a relatively stable state of aggregation, depending on the macromolecular composition of the plasma and the time they can remain without leaving the low intensity shear rate fields (Baskurt and Meiselman, 2007; Bissetti et al, 2014; Popel and Johnson, 2005).

For normal hematocrits, the aggregates that travel further from the flow axis suffer a greater number of shocks with other aggregates and with isolated erythrocytes.

They lose and gain erythrocytes more frequently than the more stable aggregates, located where the shear rates are small.

Closer to the vessel wall, the erythrocytes generally travel apart from each other, colliding with each other and with other formed elements with a frequency that is an increasing function of the local shear rate.

The mechanisms underlying the other manifestations of the self-lubricating tendency of moving blood produce the orientation of erythrocytes (already disaggregated) at intermediate shear rates and the deformation of erythrocytes at high shear rates.

This deformation includes the displacement of the membrane (attached to the adjacent cytoplasmic cortex) with respect to the cytoplasm.

By minimizing the disturbances that erythrocytes produce on adjacent plasma flow lines, these processes help to reduce isothermal energy dissipation.

However, when the deformation capacity of erythrocytes decreases sufficiently, these mechanisms are impeded and the self-fluidizing capacity of the blood decreases. At the limit, it disappears.

Two main mechanisms cause the migration of suspended deformable particles, such as erythrocytes that flow suspended in plasma.

One of them dominates low local hematocrits, such as those that can be found in the vicinity of the wall of the arteries when the global hematocrit is normal or low.

The force on the suspended particle, produced by this mechanism, increases with the shear rate, and decreases with the stiffness of the particle (Scott, 2005).

The other mechanism, leading to the so-called hydrodynamic diffusion (Davis, 1996), dominates when the local hematocrit is intermediate or high and the global hematocrit is normal.

The force on the suspended particle is produced by the asymmetry in the number of shocks it suffers.

With equal local hematocrits, this number is higher in the part of the particle surface that faces higher shear rates (Biasetti et al, 2014; Davis, 1996; Suárez-Antola, 1980).

If the particles are rigid, other migration mechanisms and other conditions come into play (Davis, 1996; Suárez-Antola, 1980; Hoskins and Hardman, 2017; Fenench and Haya, 2019; Gekle S and Bender, 2019; Gibbons-Kroeker, 2019).

This is the case of **platelets and white cells, that tend to accumulate near the inner surface of the artery wall**: this is called margination due to the push done by the erythrocytes.

Figure 6 shows measured red cell axial accumulation and platelet margination as functions of shear strain rate.

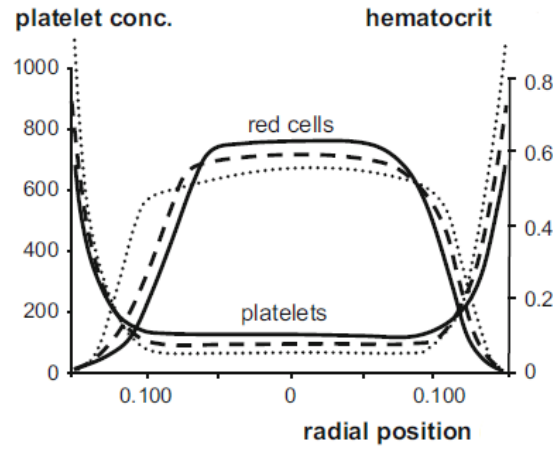


**Figure 6. Non uniform distributions of erythrocytes and platelets in blood flowing in a tube of circular cross-section. Shear rates of  $1200 \text{ s}^{-1}$  (solid line),  $760 \text{ s}^{-1}$  (dashed line),  $240 \text{ s}^{-1}$  (dotted line). Platelet concentrations in ( $\times 1000/\mu\text{l}$ ) (left ordinates axis) and hematocrits in volume formed elements/total blood volume (right ordinates axis). Radial positions in cm (Modified from Hoskins and Hardman, 2017).**

Now let us consider the relation between mass transport and the hematocrit field when the limit step is in the boundary layer between the bulk blood flow and the vascular epithelium. In a first approximation, the flux density  $J_s$  of a certain substance through the diffusive boundary layer adjacent to the artery wall can be described by this formula (Tarbell and Qiu 2006):  $J_s = k_{F-W} \cdot (C_B - C_E)$

Here  $C_B$  is the concentration in the lumen just outside the diffusive boundary layer,  $C_E$  is the concentration in the surface of the endothelium, and  $k_{F-W}$  is a fluid-wall mass transfer coefficient.

Under suitable assumptions (Suárez-Bagnasco and Suárez Antola, 2014) the following proportionality relation can be approximately applied to estimate the mass transfer coefficient knowing the shear strain rate on the vessel wall:  $k_{F-W} \propto \sqrt[3]{\dot{\gamma}_w}$

Considering that the shear strain rate can be expressed as a function of shear stress and hematocrit,  $\dot{\gamma} = h(\tau, \phi)$ , the permeability of the boundary layer verifies:

$$k_{F-W} \propto \sqrt[3]{h(\tau_w, \phi_w)}$$

It could be expected that the fluid to wall mass transfer coefficient is a decreasing function of the local hematocrit near the wall (Suárez-Bagnasco and Suárez Ántola, 2014). In the case of oxygen, it is possible to guess that the concentration just outside the diffusive boundary layer can be considered as an increasing function  $C_B(\phi_w)$  of the wall hematocrit.

The hematocrit field is rheology dependent. Then it is possible to expect that oxygen concentration near the wall is also rheology dependent.

Once the substance has reached the endothelium wall, it can react locally (as occurs with ATP that is hydrolyzed) or cross it (as occurs with oxygen and LDL).

Transport through the wall can be approximated at steady state by the formula

$$J_s = P_E (C_{s,w} - C_{e-i})$$

Here  $P_E$  represents the permeability of the epithelium,  $C_{s,w}$  is the concentration of the substance in the blood adjacent to the wall, and  $C_{e-i}$  the concentration of substance in the intima, between the epithelium and the extracellular matrix.

Two dimensionless numbers are used to describe the relative importance of transport through the blood and transport through the epithelium: the Sherwood number (Sh) and the Damkhoeler number (Da).

The Sh number is a mass transport coefficient and is defined in terms of the internal radius of the vessel  $R_V$ , the diffusion coefficient of the substance in blood  $D_s$  and the fluid to wall mass transport coefficient between the blood and the epithelium,  $k_{F-W}$  in the following way:

$Sh = \frac{k_{F-W} (2R_V)}{D_s}$  In turn  $k_{F-W}$  depends on the thickness of the diffusion boundary layer.

The Da number is associated with the permeability of the endothelium and is defined as follows:  $Da = \frac{P_E (2R_V)}{D_s}$  So these dimensionless numbers differ only in the permeability that appears in the numerator.

When Da is much greater than Sh, that is when  $k_{F-W} \ll P_E$ , the limiting step of transport is at the blood level.

Whereas if Da is much smaller than Sh, so  $k_{F-W} \gg P_E$ , the limiting step of the transport is in the endothelium.

In the case of LDL, the Da number is always much lower than the Sh number, therefore, the limiting step for the transport of low-density lipoproteins from the blood to the wall

is at the level of the vascular endothelium. This is generally observed for the transport of high molecular weight particles.

In the case of oxygen, the Da number is always much higher than the Sh number, therefore, the limiting step of oxygen transport from the blood to the interior of the wall is dominated by hemodynamics.

Figure 7 shows the variation of the Sherwood number  $Sh = \frac{k_{F-W}(2R_v)}{D_s}$  in two situations of interest in relation to pathophysiological processes in the arterial wall.

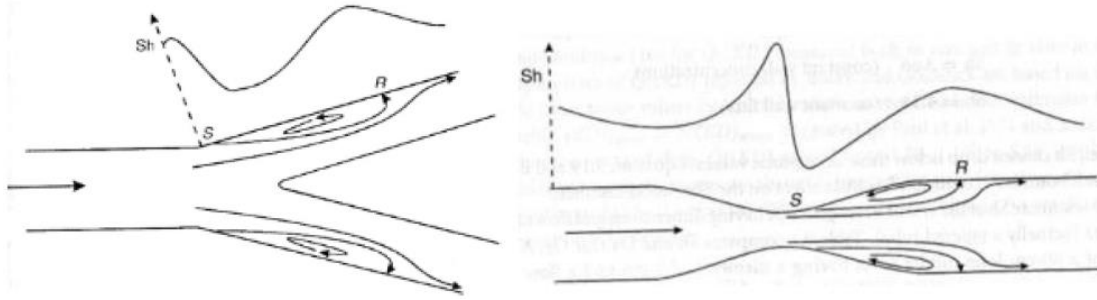


**Figure 7: Qualitative diagram of the variation in Sherwood number in an arterial bifurcation (left) and in a stenosis (right) related with the variations in blood flow. A stationary state of flow is assumed, so only spatial variations are of interest. (Modified from Tarbell and Qiu, 2006).**

Figure 7 (left) shows the disturbance in blood flow that occurs due to a bifurcation in an artery.

Drawn above the upper branch of the bifurcation, a graph is observed showing the variation of the Sherwood number on the face opposite the flow divider (where there are significant variations in the shear rate on the endothelium) as a function of the distance along the branch.

The fluid to wall mass transport coefficient  $k_{F-W}$  between the blood and the epithelium depends on this shear rate.

As the shear rate decreases (increases), the mass transport coefficient between the blood and the epithelium decreases (increases) in turn.

In places where the Sherwood number is greatly decreased, the transport of the substance towards the wall is hindered.

Figure 7 (right) shows the disturbance in blood flow that occurs due to a stenosis. Above the scheme of the stenosed vessel, a graph is observed that shows the variation of the Sherwood number as a function of the distance along the vessel.

After the stenosis, a disturbance of flow caused by the stenosis is observed.

The Sherwood number first increases accompanying the increase in the shear rate in the blood adjacent to the wall in the narrowing of the stenosis.

Then, it decreases sharply when the flow separation region starts and then gradually increases as it approaches the flow reinsertion zone.

This behavior is associated with increased transport in the narrowest region of the vessel where the Sherwood number is maximum, and with a decreased transport where the Sherwood number is minimum.

This minimum occurs when the area of greatest narrowing is passed.

### **(5) General physiological and pathophysiological aspects of blood rheology**

It has been seen, in this article and in the previous articles (Suárez-Bagnasco and Suárez Ántola, 2014; Suárez Ántola and Suárez-Bagnasco, 2015), that the global hematocrit conditions the micro-rheological properties of blood, including the processes of aggregation and axial migration of erythrocytes, and radial margination of platelets and white cells, with their consequences on the processes of mass transport between the lumen and the arterial wall, on wall repair and local infection control.

The combination of a pressure difference, acting as a driving force, with viscous dissipation, acting as a brake, together with the properties of plasma and the population of blood cells, in the framework of the restraints to the velocity fields introduced both by boundary conditions and the geometry of the conduits, allow non-equilibrium phase transitions that explain the self-fluidification of blood when shear velocities are high enough and the increase in viscosity when shear velocities are low enough (Schmid-Schönbein, 1996).

The self-fluidification begins by the disaggregation of the rouleaux and continues by the self-orientation and deformation of erythrocytes, in a process that tend to be first self-enhanced and then to stabilize, if the pressure difference (always above a critical value) and other conditions remain unchanged.

The self-impeding of blood proceeds like the processes of self-fluidification but taken in the reverse order. If the pressure difference (always below the critical value) and other conditions remain equal, it is also first a self-enhancing process and then tends to stabilize (Schmid-Schönbein, 1996).

An overall reduction in intravascular volume, rapid enough and significant enough, tends to acutely increase both the overall hematocrit and the overall plasma protein concentration.

This reduction can be caused either by non-hemorrhagic fluid losses (very intense perspiration or leakage through the urinary and gastrointestinal tracts), or by the contraction of the muscles of the arterial walls caused by a catecholamine discharge (in a situation of stress) with a significant increase in intra-luminal pressure, followed by fluid displacement into the tissues.

Increases in the concentration of formed elements and macromolecules, ultimately due to the non-hemorrhagic decrease in blood volume, favor the aggregation of erythrocytes (elevated hematocrit and fibrinogen concentration), and generally increase the viscosity of the blood .

Then come the compensatory reactions, tending to restore homeostatic values.

Together with the global hematocrit, plasma viscosity is a fundamental parameter in determining the rheological behavior of blood in vivo (including axial accumulation of erythrocytes), both under normal and pathological conditions (Cowan et al, 2012; Sloop and Garber, 1997).

Here we refer to both the global hematocrit and the plasma viscosity, determined from a sample drawn from a large vein.

Plasma viscosity is statistically correlated with global concentrations of plasma lipids and proteins (cholesterol, triglycerides, fibrinogen, globulins) (Apostolidis and Beris, 2015; Moreno et al, 2015).

It is also statistically correlated with the global concentrations of signaling molecules of renal origin (erythropoietin), pituitary (growth hormones), immune (cytokines), adipocyte (interleukins) and others (Brun, 2002).

In the case of coronary atherosclerosis, there is evidence to suggest that the local secretion of hormones (such as aldosterone) by the heart tissue and the activity of the nerve network associated with the heart (a network that some physiologists call the "little brain in the heart" ) influence the development of the disease (Suárez-Bagnasco, 2014). From what has been said previously in the present work, it is possible to conjecture that these local secretions could contribute to modify the local rheological properties of blood in the cardiac circulatory subsystem.

In general, there is currently general agreement on the core concepts in physiology and pathophysiology, including the self-organization of emergent levels in a hierarchy that spans from atoms to ecosystems, including cells, tissues, organs, individuals, and populations (Baffy and Loscalzo, 2014).

The interaction between the immune, nervous, and endocrine systems can be interconnected with mental functions using the discipline known as psycho-immuno-neuroendocrinology (PINE), both under normal and pathological conditions (Jerry, 1996; Suárez-Bagnasco, 2014).

To approach the human being as a bio-psycho-social unit, the PINE focuses on the level of physiological systems, in the study of anatomical and functional interrelationships. The level corresponding to the physiological systems constitutes the integrating nucleus, the reference level, from which the levels below (organs, tissues, cells, subcellular level) and above (psychological, sociocultural) are considered (Suárez-Bagnasco, 2014).

In principle, the PINE provides a conceptual framework that allows addressing possible connections between hemorheology and hemodynamics with psychosocial aspects of human life.

PINE considers that the organization of a system made up of numerous interacting subsystems can change abruptly when a parameter crosses a threshold.<sup>4</sup>

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<sup>4</sup> known as a control parameter in the synergetic version of systems theory.

The interactions between subsystems, when the control parameter reaches a critical value, become stronger and more far-reaching. The resulting cooperative effect generates a new structure. Thus, supramolecular dissipative structures are formed from molecular interactions, and these can interact, originating superstructures, in a chain of progressive complexity. So, an emergent level can be thought of as generating a set of constraints within which the emergent entities of lower levels are embedded. When a complex system emerges, the genesis of a level presupposes the prior appearance of lower levels. This level, in turn, makes possible the appearance of higher levels that, once constituted, restrict it in turn. When a complex system becomes disorganized, the process begins with the disappearance of the highest emergency levels and progresses with the disappearance of the levels below it (Suárez-Bagnasco, 2014).

In particular, the main underlying issue in the discussion of the possible physiological and pathophysiological consequences of the non-uniform distribution of blood formed elements in the framework provided by PINE is the identification of the constraints that a reference level such as the level corresponding to the physiological systems, in a hierarchy of systems, imposes as conditions within which the processes in the emergent entities of lower levels (such as molecular subsystems, subcellular structures, cells and tissues) develop, and the way in which the processes at the reference level of physiological systems are in turn constrained by the psychological level. Without intending to go into detail about the possible mechanisms involved, in what follows we mention some experimental results that relate the psychological level to the level of physiological systems and levels located below in the hierarchy of systems.

In healthy subjects, acute mental stress activates coagulation and fibrinolysis within physiological ranges. In patients with atherosclerosis, the response to acute stress promotes a state of hypercoagulability.

Chronic psychosocial stress is related to hypercoagulability reflected in the increase of procoagulant molecules and the reduction of the fibrinolytic capacity (Ring, 2008).

In situations of psychological stress, a more prolonged procoagulant response has been described in adults with a low socioeconomic level than in adults with a higher socioeconomic level, which could contribute to an increase in cardiac risk in adults with a lower socioeconomic level (Steptoe et al, 2003).

Factor VIII and plasma viscosity (and hence blood viscosity) have been found to remain elevated for 45 minutes post-stress (Steptoe et al, 2003).

Overall blood viscosity and overall hematocrit (both determined from a sample drawn from a large vein, subjected to low, medium, and high shear rates to determine viscosity) are significantly increased in people with major depressive disorder (Wong, 2008).

Although the presence of cardiovascular risk factors influences the rheological properties of the blood, aging itself, through both inflammatory and lipid metabolism changes, is associated with a deterioration in blood functions, both macro rheological and micro rheological (Vayá et al, 2013).

## **(6) Considerations from the point of view of Evolutive Biology**

From the point of view of evolutionary biology, aggregation as a mechanism that intensifies the axial accumulation of erythrocytes and reinforces the self-fluidifying properties of the blood, is observed in athletic species, but not in sedentary ones (Bishop et al, 2001).

In athletic species, such as *Homo sapiens*, the increase in oxygen demand may require a significant increase in the flow that irrigates certain tissues.

An increased velocity profile produces disaggregation of erythrocytes and lowers the viscosity of the blood in the arterioles and venules.

This decrease in hemodynamic resistance, in combination with the regulation of vascular diameter, allows an increase in flow in that territory without the need for a comparable increase in pressure and energy dissipation.

Under normal conditions, the axial accumulation pattern reaches a saturation value at low flow velocities with respect to the physiological velocities observed in most vessels. Thus, the physiological limits of blood output are generally above the mentioned saturation value (Suárez-Antola, 1980).

Intensified axial accumulation is accompanied, during evolution, by the appearance of certain special anatomical structures in some secondary arteries, which allows them to transport blood with a higher average concentration of hemoglobin than the primary arteries from which they originate.

Figure 8 shows one of these anatomical structures, in this case in the embouchure of a branch of the human uterine artery. These anatomical peculiarities are not general throughout the human circulatory system: for example, they are not present in the branches of the mesenteric artery.

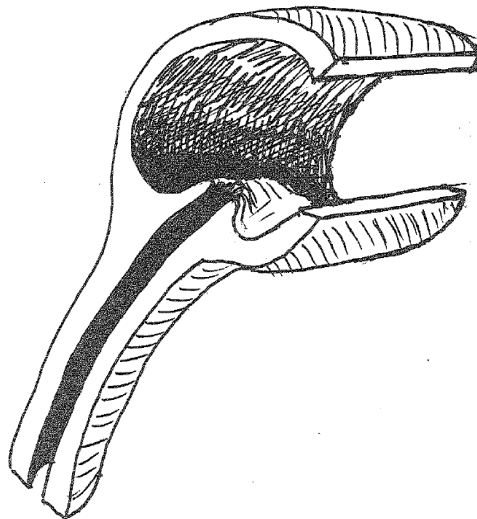


**Figure 8. Anatomical structure showing the mouth of an artery that leaves the main trunk of the uterine artery. It allows blood to be collected from the central region of the main artery, where the local hematocrit is higher than the values taken by said hematocrit in the area near the wall of the uterine artery (Suárez-Antola, 1980).**

Secondary arteries whose mouths do not have these anatomical structures carry blood with an average hemoglobin concentration equal to or lower than that of the main artery. With this, a certain degree of selection is achieved in the properties of the blood that flows to different capillary territories.

Finally, evolutionary biology provides an interesting perspective on an inevitable consequence of the branching structure of the arterial tree: the presence of pro-atherogenic disturbances both in the flow and in the mechanical stresses inside the wall.

These pro-atherogenic disturbances appear in the places where there are bifurcations, ramifications, curvatures, or anatomical structures such as the carotid sinus.

Despite some compensatory anatomical modifications (among them, the moderate thickening of the wall at the mouths of the branches and at the bifurcations), there is evidence that in some of these sites a low level of chronic inflammation is maintained, not only in adult organisms but also in developing organisms (Hahn and Schwartz, 2009).

When in people it is combined with risk factors (such as diabetes, obesity, hyperlipidemia, sedentary lifestyle, smoking, stress), an atherosclerotic disease can develop, culminating in the formation of plaques and eventually an ischemic event (Coppola and Caro, 2009; Hahn and Schwartz, 2009; Nichols et al, 2011; Thubrikar, 2007).

In the case of primitive man, the time from development of an atherosclerotic disease to a life-threatening event, was greater than or at most of the order of life expectancy. Due to this fact, the evolutionary solution that involves branching of the arterial tree would not imply a limitation for the organism.

On the other hand, the solution based on a tree seems difficult to avoid in view of what has been said, regarding Bejan's nonequilibrium thermodynamic law, in section 2 of this article.

From the synchronic point of view, which only considers the situation in the present, the anatomical and physiological characteristics that are observed in the current species, are not necessarily optimal solutions.

But when these characteristics are considered from the diachronic point of view, which considers the succession of historical situations and the limitations presented by possible evolutionary discontinuities, it is noted that they are the result of the modification of what is available in each stage to remedy a specific need.

In any case, starting from the stage of human development in which life expectancy increased significantly, in a much shorter period than evolutionary time scales, the consequences that lead to pathologies associated with the solution to the problem of distributing blood to tissues carried out by branching of the arterial tree, became limiting of this life expectancy.

## (7) Conclusions

-There is growing evidence, obtained by experimenting with animals and through clinical observation in humans, about the importance of the rheological behavior of blood, including axial accumulation of erythrocytes, in the degree of perfusion of tissues.

-It is necessary to investigate further the processes of aggregation, orientation, and deformation of erythrocytes, considering that they can influence endothelial function and hemostasis mechanisms.

-Since the aggregation of erythrocytes can be increased during pathophysiological processes such as those that occur in infectious, hematological, circulatory, and metabolic diseases, its understanding is also important from the medical-clinical point of view.

-The results of computational fluid mechanics work carried out in models of the aorta and carotid bifurcation, with and without stenosis and aneurysms, suggests that at sites where the axial accumulation of erythrocytes is combined with secondary flows can produce a synergy between both processes (Biasetti et al, 2014) (Auricchio et al, 2019). According to the results of the digital simulation, this synergy leads to a decreased local hematocrit with a lowering in average shear stress on the artery wall, precisely in the regions known to be prone to atherosclerosis.

-Margination of stiff particles improves the function of the cardiovascular system because the platelets and white cells are pushed towards the wall and accumulate in the region where they accomplish their functions: endothelial repair and thrombus formation in the first case and crossing the endothelium to fight infections and their consequences in adjacent tissues.

- The self-fluidification of blood at high shear rates and the self-impeding of flow at low shear rates can be interpreted as non-equilibrium phase transitions in flowing blood, under the combined effects of driving forces and dissipative processes.

- In a neighborhood of the arterial wall, the shear velocity field influences the mass transport between the fluid and the endothelium through a diffusion boundary layer, adjacent to the endothelium.

The regions with low shear velocity in the adjacencies of the endothelium present lower permeabilities in the convective-diffusive boundary layer.

This influence acquires great importance when the limiting passage to mass transport is in this boundary layer.

-There is evidence that this occurs in the transport of oxygen, ATP, bradykinin, angiotensin, and other effectors that are degraded or chemically modified on the surface of the endothelium.

In relation to the supply of oxygen to the wall, a decrease in the permeability of the boundary layer can cause local hypoxia in the intima and in part of the media proximal to the lumen, which in general does not receive input through the vasa -vasorum.

-When chemical species are transported by blood cells, as is the case with oxygen transported by erythrocytes, a decrease in the local hematocrit near the wall, due to axial migration of the formed elements, can decrease fluid-wall transport with possible physiological and pathophysiological consequences.

-As the evidence indicates that the limiting passage for LDL transport from the lumen to the wall is in the vascular endothelium, the shear rate in the adjacencies of the endothelium does not affect the transport of LDL in the boundary layer.

However, the shear stress on the endothelium modulates transport through the endothelium.

The incorporation of LDL by the arterial wall is greater in the regions with low and oscillatory shear stresses because it increases the permeability of the endothelium to LDL. In addition, low shear stress results in increased adherence of leukocytes (especially monocytes) to the surface of endothelial cells due to changes in the phenotype of the latter.

For these reasons it seems to be important to consider the non-Newtonian rheological behavior of blood.

The spatial variations of the concentrations of the blood formed elements and their level of aggregation also influence the relationship between the shear stress and the shear rate.

-The changes in blood rheology seen in people with major depressive disorder could contribute to increase their risk for cardiovascular disease.

-When the biomechanical description is extended to the identification and analysis of the autocrine, paracrine, and immuno-neuroendocrine signaling mechanisms, with their metabolic concomitants and modified phenotypic expression, which accompany and enable the initiation and development of responses, hemodynamic and hemorheological, it is noted that the rheology of the blood can not only vary due to numerous processes, both normal and pathological, but can also condition them.

A psychosomatic approach could be of interest in a holistic approach to hemorheology and hemodynamics.

-It can then be expected that the axial accumulation of erythrocytes with their physiological and pathophysiological modifications constitutes one of the relevant processes to understand the local effects of the modulation of blood micro-rheology through psycho-immuno-neuroendocrine interactions.

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